Determination of the Minimal Clinically Important Difference of the UNC Dry Eye Management Scale

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ABSTRACT

BACKGROUND: Dry eye disease (DED) is a common, chronic ocular surface disease affecting millions of Americans; it can severely diminish quality of life (QOL). Many patient-reported outcomes (PRO) questionnaires have been developed to assess DED, but few have established a minimal clinically important difference (MCID) in accordance with FDA guidelines.

OBJECTIVE: To establish an initial estimation of the MCID of the UNC Dry Eye Management Scale (DEMS) and assess patient perceptions of symptom change versus score change.

METHODS: I recruited 33 patients who had a prior DEMS score from a UNC ophthalmology cornea clinic in Chapel Hill, NC for study in the months of May and June 2014. I compared patients' change in the DEMS scores from the most recent prior visit to patient-reported assessments of change in symptoms at the time of this study. Using anchor-based methods to determine an MCID, I obtained linear regression coefficients from the comparison to be my estimation of the MCID. I also recorded clinical assessments of the patients' disease severity, and I administered another questionnaire to assess patient perceptions of score change as it relates to symptom change.

RESULTS: All 33 patients in this first attempt to establish MCID were included in analysis (33.3% male, 67.7% female, mean age 60.5 years). Anchors were correlated with DEMS score changes. The MCID ranged from ½ point using linear regression analysis to 1 point using descriptive statistics. Patients felt that a change of approximately 2 points was needed to represent an improvement/worsening of symptoms. The UNC DEMS had modest correlations with clinical tests.

CONCLUSIONS: The UNC DEMS is a valid, responsive PRO instrument that can be used easily in the clinic to aid in the management of dry eye disease over time.

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INTRODUCTION

Recognition of the value of patient-reported outcomes (PRO) in health care and health care research has been growing. The importance of PROs is reflected in growing policy guidance from the Food and Drug Administration (FDA) and provisions in the Affordable Care Act (ACA) such as the creation of the Patient-Centered Outcomes Research Institute (PCORI).[1–4] As a result, the necessity of developing measurable PROs for clinical trials and health care has led to increasing numbers of PRO instruments over the past decade in many domains. The field of ophthalmology is no exception. These instruments have particular value in managing non-curative or chronic diseases.

One common, chronic, ocular disease responsible for a large proportion of eye clinic visits each year and a substantial burden of disease is dry eye disease (DED). Dry eye disease affects millions of adults over age 50 and is associated with symptoms such as pain, burning, grittiness, tearing, and light sensitivity; it can harm patients' quality of life (QOL).[5–9] In fact, time trade-off methods of estimating the burden of disease have shown that moderate to severe dry eye disease is felt to be as or more burdensome than dialysis, severe angina, and hip fractures.[10] Unfortunately, many studies have found a relatively poor correlation between clinical assessment of disease severity and patient-reported symptoms.[11] This lack of correlation makes patient-reported assessments of symptom burden quite important in treating and managing the disease. Effective monitoring of disease severity and the appropriateness of treatments could benefit from a measurable patient-reported outcome that can be followed over time. Therefore, many questionnaires that aim to evaluate relevant domains within dry eye disease have been developed. However, the clinical utility of many questionnaires is still uncertain.[12]

BACKGROUND AND SIGNIFICANCE

Over twenty dry eye symptom questionnaires are documented in the current literature; however, a recent review identified only six capable of assessing quality of life.[13] Two instruments, the Ocular Surface Disease Index (OSDI) and the Instrument of Dry Eye in Everyday Life (IDEEL) have undergone robust validity and reliability studies and have been used in clinical trials.[14–18] The most recent version of the OSDI is a 12-item questionnaire assessing three domains: symptom frequency, symptom bother, and environmental triggers.[14,19] The questionnaire is scored on a scale from 0 to 100 and requires the use of an algorithm and scale to determine a patient's dry eye disease severity. The IDEEL is a 57-item questionnaire developed to assess 3 domains: "dry eye symptom-bother, dry eye impact on daily life…and dry eye treatment satisfaction" (p.1).[16] However, length and/or multi-step interpretation of scores may make both instruments challenging for use within the context of a busy eye clinic.

Therefore, our colleagues at UNC developed the UNC Dry Eye Management Scale (DEMS), which was born out of the need for a valid, reliable, easy-to-administer, and easy-to-interpret instrument that can assess both patient-reported symptoms and their effects on daily life. The UNC DEMS is a single-item instrument that asks patients to rate their symptoms and those symptoms' effects on daily life on a scale from 1-10. The instrument was created for use in the clinical setting, with emphasis placed on the importance of ease of use and quick interpretability. It was developed in accordance with the PROMIS methodology for development of patient-reported outcomes (PRO) instruments and, in recent work, the UNC DEMS has been shown to be both valid and reliable, strongly correlating to scores generated by the current gold standard measure, the OSDI.[2]

However, we recognize that the utility of a PRO tool to be used for monitoring disease severity and as a guide for treatment regimens depends largely on its ability to

detect change over time and the meaning of that change. Groups like the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) and the Food and Drug Administration (FDA) have recognized the importance of developing and choosing appropriate PRO tools for research.[1,3,20–23] Included in their guidance is the necessity for determining the responsiveness of an instrument – its ability to detect change over time. The FDA recommends determining "a score change in a measure, experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit," often referred to as the minimal clinically important difference, or MCID.[22] As a result, our efforts in further validating the UNC DEMS are now focused on the next portion of our research – determining the MCID.

METHODS

Patient recruitment and participation

Currently, just one ophthalmologist (R.D.) regularly administers the DEMS to dry eye patients seen at UNC ophthalmology outpatient clinics. Consequently, with the guidance of my faculty advisors, I recruited all 33 patients for this study from this one provider during the months of May 2014 and June 2014. To be included in the study, patients must be 18 years of age or older, have a diagnosis dry eye disease (ICD-9 375.15 - tear film insufficiency), and have at least one previously documented DEMS score. I wanted to evaluate the responsiveness of the DEMS over time; therefore, I did not exclude patients based on etiology of DED. Because the DEMS has only been validated in English, I recruited only English-speaking patients for the study. After receiving UNC IRB approval of the study, I began to identify eligible participants at regularly scheduled clinic appointments. I then obtained consent from the patients who agreed to participate in the study. I collected age and sex data along with date and score of the most recently recorded DEMS score. If available, I also recorded prior clinical assessments of dry eye disease including Schirmer tear production test, tear break-up time (TBUT) and Oxford grading scheme for dry eye score from the corresponding visit.

Patients underwent their usual clinical assessment and care during their visit for dry eye disease, including administration of the UNC DEMS during initial work-up by the technician prior to evaluation by physician and/or researcher. If the UNC DEMS had not been administered prior to the patient being approached for participation in the study, student researchers would first administer the DEMS before continuing with the study data collection. Those administering the UNC DEMS were instructed to do so using the following statement: “Using the examples below (pointing to UNC DEMS scale), please circle the one number that best describes your dry eye symptoms and how they affect

your daily life over the past week." The UNC DEMS was then scanned into the medical record and the score is recorded within the patient's medical record for that visit. The UNC DEMS questionnaire can be found in Appendix B.

Clinicians, or researchers with clinician supervision and confirmation, also conducted routine assessments for tear production and tear film quality, as well as an evaluation of the ocular surface. Evaluations were made via Schirmer test, evaluation of tear breakup time, and ocular surface evaluation via fluorescein staining using the Oxford grading scheme for dry eye respectively. Patients' participation in the study did not influence the clinical or therapeutic course of disease management. To compensate participants for their time, we offered to enroll them in a lottery for a $10 gift card at the conclusion of the study. We determined winners by random number generator using de-identified patient information, and gift cards were mailed to those selected from the lottery.

Dry Eye Symptom Change Questionnaire

Based on prior research and literature on acceptable methods for determining the responsiveness of patient-reported questionnaires, and with the guidance of my faculty advisors, I developed a single-item, Likert scale questionnaire to serve as an anchor for within-patient global transition assessment, or what we call the global change assessment (GCA).[22,24–26] The questionnaire, called the Dry Eye Symptom Change Questionnaire (DESCQ), asks patients, "compared to your last visit, how are your dry eye symptoms now?" Patients responded by choosing one of the following global transitional assessments: "much worse, somewhat worse, a little worse, the same, a little better, somewhat better, or much better." The DESCQ also includes questions about patients' perceptions of symptom change and their current therapeutic and/or behavioral methods for managing their disease.

To serve as an additional reference for measuring patients' beliefs on symptom change as it relates to their DEMS score, we also asked patients the following questions:

> "How many points would your score have to change to show that you felt like your symptoms were getting *better*? That is, how much change would be a meaningful improvement in quality of life for you?"

> "How many points would your score have to change to show that you felt like your symptoms were getting *worse*? That is, how much change would mean that your symptoms were making your quality of life worse?"

> "If you could choose a number on the UNC DEMS that would be your *goal score* for treatment of your dry eyes – the place you'd like to get to – what would that number be?"

The questionnaire in its final administered version can be found in Appendix B.

Statistical Analysis

To be included in the analysis, participants must have had a previously recorded DEMS score and must have met all other inclusion criteria. Because I asked patients to consider their symptoms and how they have changed since last visit, I recorded only the most recent score for those patients with multiple prior DEMS scores. For those reporting a range of numbers (e.g. "1 to 2 points") rather than a single score for either their prior DEMS, current DEMS, or any other question, I used the average of the range reported for the statistical analysis. For example, if a patient reported "1 to 2 points," I used "1.5" as the value for data analysis. I initially scoured the data for missing values,

which I replaced with last known value carried forward. If no known previous values were available, the missing entry was omitted from the analysis.

I compared the prior DEMS score to the current DEMS score and determined the difference in scores. Scores representing less severe disease are represented by lower numbers on the UNC DEMS with 1 being the lowest severity and 10 the highest. I chose to calculate the difference by subtracting the previous DEMS score from the current DEMS score. Therefore, a negative change represented a patient-reported improvement and vice versa. This scoring choice dictated that I would base the DESCQ on a Likert scale centered at numerical "0" to serve as anchors for patient-reported global change assessments (GCA). The responses "much worse, somewhat worse, a little worse, the same, a little better, somewhat better, and much better" corresponded to an assigned numerical value of "-3, -2,-1, 0, 1, 2, or 3" respectively. As such, a relationship could be assessed between patient-reported symptom change (GCA) over time and the actual change in DEMS score.

I recorded clinical evaluations of disease severity using Schirmer test, TBUT, and Oxford grading scheme for each eye individually and then averaged scores for each eye to enter into the statistical analysis as a single variable for each test. Rather than convert test values into arbitrary categories of normal or gradations of severity, my advisors and I decided to treat each test as a continuous variable for correlation analysis.

This study's primary outcomes were the change in DEMS score and the patient-reported GCA. Secondary outcome relationships included the association of scores with age, sex, number of days since last visit, DEMS score at last visit, Schirmer test, TBUT, Oxford score, patient responses to perceptions of smallest incremental improvement/worsening in DEMS score, and goal DEMS score.

Because patients seen in the clinic are undergoing treatment for their dry eye disease, we expected most to report improvement over time or at least no worsening. Therefore, to account for the likely small sample sizes within the "worsening" GCA categories, I folded data for statistical comparisons across GCAs by using the magnitude of change for each incremental category regardless of the direction. In this manner, data for "a little worse" were paired with "a little better," "somewhat worse" was paired with "somewhat better," and "much worse" paired with "much better" to create 3 categories of incremental change. All other analysis, including estimation of the MCID, was done using unfolded data.

Estimation of the MCID. Developers of the OSDI and the IDEEL have employed collapsing of subgroups and folding of data to account for small sample sizes within groups to improve their statistical power during analysis.[15,17] Using a method similarly reported by Miller and colleagues, I used linear regression modeling to establish our estimation of the MCID.[15] Although the authors used folded data for their linear regression modeling, I opted to not fold the data for this modeling. Linear regression analysis allows us to use the entire spectrum of change in patient-reported global change assessments regardless of direction and magnitude, thereby eliminating concern about small sample size within subgroups. In this way, my estimation of the MCID represents the predicted change in DEMS score as a function of the patient's rating of symptom change.

I initially examined the data for correlation between actual changes in DEMS score and reported global change assessments using Spearman's rank correlations to assess the legitimacy of the anchors in the data analysis. I also examined correlations between all other independent variables to ascertain whether the independent variables are collinear prior to assessing their weight in estimating the MCID. After bivariate

analysis to characterize the unadjusted associations between the study variables of interest (age, sex, days since last visit, and previous DEMS score) and the change in DEMS score since the last visit, I examined their independent association using a multiple linear regression model. I first conducted a multiple linear regression analysis including all independent variables regardless of significance. Then, in a step-wise fashion, I dropped those variables without a statistically ($\alpha = 0.05$) or clinically significant (>10% change) relationship to the change in DEMS score. I used the final, reduced model including the most significant variables for estimation of the MCID using coefficients from the linear regression fit to the data.

Correlation of DEMS with clinical findings. The likelihood of non-normal distribution of data based on DEMS scores and patient-reported GCA directed me to use Spearman's rank correlations to assess the relationship between patient-reported disease severity via DEMS score and clinical assessments of disease severity via Schirmer, TBUT, and Oxford scores. Statistical significance is achieved at $\alpha = 0.05$.

RESULTS

This analysis results from exploring the data produced by a total of 33 participants. The majority of participants were women (67.7%) and the average age of all participants was 60.5 years. On average, patients went 122.5 days between visits and had an average prior DEMS score of 5.33 (Table 1). All data were available for 30 of the 33 patients (90.9%). Those who were missing data did not have last values to carry forward and were missing either all three clinical assessment tests (1 patient) or deferred the Schirmer test (2 patients). No patients were missing DEMS scores and all fully completed the DESCQ.

The vast majority of patients reported that they felt their symptoms were the same or better, with only 4 patients reporting a worsening of symptoms since their last visit, and none said “much worse” (Figure 1). Correlations of DEMS score change with the GCA showed a moderate, statistically significant correlation, validating the use of our anchors for this study (Table 2). I also found that compared to other independent variables, the DEMS score change was statistically significantly correlated with the number of days since the last visit as well as the last DEMS score. Age and sex were not correlated with the change in DEMS score.

Table 3 shows the average score change using folded data comparing patient-reported global change assessments. Literature has described using the mean score change for the smallest GCA anchor as an arbitrary method for determining the MCID.[24–26] The average change for those rating their symptom change to be “a little better/worse” was 1.09 (n = 11). By this method, the MCID would be approximately 1 point on the DEMS scale. For the next incremental change rating of “somewhat better/worse,” the mean score change was 1.81 (n = 8), which shows an expected increase in magnitude in score change of almost 1 point paired with a greater improvement/worsening of symptoms. However, the largest change in symptom

category “much better/worse” had a mean change in score of only 1.00 (n = 6) Although the trends in score change appear to be consistent with an expected increase in magnitude of change with each incremental rating of symptom change, the smaller sample size for this category likely limits the certainty of our findings.

Patient perceptions of symptom and score change – responses to DESCQ

When I interviewed patients using the DESCQ, I also wanted to explore patient perceptions of how a meaningful change in symptoms would be represented in the score change on the DEMS. The frequency of patients’ estimations of a meaningful score change is reported in Figure 1. Interestingly, patients reported that their DEMS score would have to improve by 2.0 points on average to show that their symptoms were getting better (Table 4). Conversely, patients reported that on average a 2.3 point score change in the opposite direction would show that their symptoms were getting worse. When I asked what their goal score for treatment would be, the vast majority of patients reported wanting to get to the lowest score possible of 1 point (Figure 2). The average goal score was 1.4. No patients reported a current DEMS score of 1.

The relationship between the independent variables and the change in DEMS score over time shows that longer time between visits was correlated with worsening DEMS scores since last visit. Linear regression results produce a statistically significant trend of an estimated worsening of 1.3 points for every 100 days since the last visit ($p = 0.003$) (Figure 3). In this sample of patients, the average time since last visit was 122.5 days. When I dichotomized by time since last visit to this mean, dividing patients into those who had gone $\geq$120 days since last visit (N=14) and those who waited less than 120 days between visits (N=19), patients with less time between visits had an average score change of -1.45 points, while those waiting longer had an average score change of +0.17 (Table 5). Paired t-test revealed that this was a statistically significant difference

of means (p = 0.006). However, those who had ≥120 days since the last visit also tended to have higher DEMS scores at their last visit (Table 6). The relationship between the worsening in DEMS score and length of time between visits maybe be partially explained by the higher scores at the last visit, but this does not explain why those with worse DEMS scores would wait longer before returning to their ophthalmologist. Linear regression analysis of the DEMS score change and the last DEMS score also shows that those with higher DEMS scores at their previous visit tended to show greater improvements (Figure 4). Clinically, those with better managed symptoms and, thus lower DEMS scores, tend to follow up less frequently, which would be consistent with smaller improvements that are closer to goal scores over longer periods of time.

As literature has often shown that clinical assessments of dry eye disease can be poorly correlated with patient-reported symptoms, I also wanted to evaluate the correlation of clinical signs of disease with what patients reported via their DEMS scores.[11] I was able to achieve statistically significant correlations between the DEMS scores and all three clinical tests (Table 7). Though not strongly correlated, the results of each test were moderately associated with DEMS scores when treated as continuous variables ranging from -0.3559 for TBUT to -0.4045 for Schirmer test. Higher Schirmer score represent increasing amounts of tear production and longer TBUT suggests healthier tear films. Conversely, higher Oxford scores indicate higher amounts of fluorescein staining, which indicates more severe dry eye disease. Therefore, the direction of correlation for each test with the DEMS is what we would expect to see, and the findings further validate the utility of the DEMS as a meaningful health outcome.

Figure 5 is a plot of actual DEMS score change against how patients reported their symptoms had changed since their last visit. An unadjusted linear regression model yielded a statistically significant relationship (R-squared 0.18, p = 0.014) with a

beta coefficient of -0.54 (CI -0.97, -0.12), which represents our estimation of the MCID. As our earlier data analysis had shown, the DEMS score change may also be a function of both the length of time since the last visit as well as the score at the last visit. Therefore, we ran a linear regression analysis adjusted for both days since last visit and the previous DEMS score. The adjusted regression yielded similar values and a stronger strength of association (beta = -0.56; CI -0.99, -0.13; R-squared 0.43; p = 0.013). Based upon our linear regression analysis, we estimate that the MCID for the UNC DEMS is approximately one half (½) a point on a 10 point scale, making the UNC DEMS capable of giving both patients and clinicians a fine-grained indication of improving or worsening disease.

DISCUSSION

The oft-described lack of correlation between clinical signs and patient-reported severity of symptoms in dry eye disease makes managing the disease difficult.[11] That dry eye disease cannot be cured further contributes to the challenge, which then requires that physicians and patients alike be engaged in a long-term process of disease management. Without a meaningful health outcome measurement to guide the treatment course physicians may face additional obstacles and uncertainty of treatment effectiveness and/or appropriateness. Therefore, many dry eye PRO instruments have been developed to address such challenges.[13] However, the responsiveness, or ability to detect a change over time, and the minimal clinically important difference of a change in PRO measure for the vast majority of these instruments has not been evaluated. The FDA has recognized the importance of developing PRO instruments for both clinical trials research and drug label claims, and has established guidelines for PRO instrument development, including the establishment of an MCID.[3,22,23] Furthermore, the International Dry Eye WorkShop (DEWS), a well-recognized group that produces timely publications with summaries of extensive data and literature analysis within the field of dry eye, argues that "clinically meaningful changes in questionnaire scores need to be defined "(p. 105)[27] In accordance with such guidelines, we have taken on the challenge and responsibility of developing and validating the UNC DEMS and, now, its MCID.

My faculty advisors, my fellow investigators, and I not only wanted establish an MCID using acceptable methods described in literature, but we also wanted to assess patient perceptions about the magnitude of meaningful score changes as well as a goal score for treatment on the UNC DEMS. We chose an anchor-based method using within-patient global transitions assessment, or what we called the GCA. We then compared the patient-reported magnitude and direction of symptom change since the last visit and compared that to the actual changes in DEMS score. Using a method

similar to that employed by the developers of the MCID for the OSDI, I chose to use the coefficients from a linear regression analysis to estimate the MCID. I also looked at the average score change for those reporting the smallest incremental change in symptoms from last visit, as well as what patients say is the change in DEMS score that would mean an improvement/worsening of symptoms to them. Based on my linear regression results, I estimated that the MCID of the UNC DEMS is about half a point. However, I also recognize that the average score change for those reporting "a little better/worse" was approximately 1 point, and patients themselves said that an average of 2 points was necessary to reflect an improvement or worsening of symptoms.

Several factors may contribute to our findings. First and foremost is the small overall sample size, and even smaller sizes for between group comparisons. We feel that using all 33 data points within a linear regression model gives us better statistical confidence in our findings, whereas group-by-group mean comparisons with small sample sizes and wide standard deviations limit the certainty of the results of those tests.

Second, another limitation to using within-patient global transition assessments as anchors for establishing an MCID is that it relies on the patient's ability to recall the time period between the current visit and the *most recent* prior visit with some subtlety. For example, some patients may have considered their symptoms at the beginning of their treatment course and report feeling "much better" since that time rather than the time of their *last* visit, which may have only been incrementally better. This may explain why some patients said they were feeling "much better" yet had small or no improvement in their scores. This challenge is inherent to using within-patient global transition assessments for anchor-based determination of MCID, and is not unique to our study.

A third caveat to our estimation of the MCID is that it relies on the proper administration of the DEMS. During the study, I found in a few cases that technicians

trained to properly administer the DEMS had not done so according to our instructions. Although the UNC DEMS is a scale from 1-10, it is not equivalent to an arbitrary symptom severity rating from 1-10. Rather, the numerical choices are anchored by examples provided on the scale and it has been validated only as an administered questionnaire.

Fourth, by using a linear regression analysis to estimate our MCID, I then assume that each incremental change is perceived to be equivalent anywhere along the scale. For example, a 1-point change from 9 to 8 would be equivalent in the perceived change in symptoms as a change in score from 3 to 2. Subsequently, the analysis also assumes that the MCID is the same for movements in score in either direction on the scale. As such, we assume that a ½ point worsening is equivalent to a ½ point improvement, in terms of patient perceptions of symptom change. Further testing should help unravel these questions of directionality and floor and ceiling effects.

Additional considerations may contribute to the results of this study. On the DESCQ, patients were not specifically asked about what the *smallest* change in DEMS score would be to reflect the smallest meaningful or noticeable change in symptoms. Although we would expect the answer to this question to be less than the mean of 2 points that we discovered, we also feel that asking in this manner would be slightly leading. Our questions allowed patients to answer in an unbiased fashion and may in fact represent true patient perceptions. However, there is a possibility that some patients had difficulty understanding the meaning of the question and may have been providing responses relative to their actual DEMS score, which would bias our results towards a larger mean change. A few patients did require clarification questions and there is no way to know that patients accurately understood how to answer the questions. Despite these uncertainties we feel that the vast majority of patients

answered the questions with an appropriate understanding and the questions did capture what patients believed to be meaningful changes in score.

We also did not consider the length of time patients have been coping with their dry eye disease, which may also have some relationship to the magnitude of change from visit to visit. Those with the disease for longer lengths of time may have reached what they have come to accept as reasonable DEMS scores and may be less likely to change from visit to visit. We may be able to infer this from our data showing that patients with higher DEMS scores were also more likely to have bigger improvements in their score. Other limitations include not blinding researchers assessing clinical severity of disease to prior/current DEMS scores.

One particular finding that may not be surprising, but may provide some useful evidence for frequency of visits for managing dry eye disease, is that those who had gone longer between visits were more likely to report either no change or a worsening of their symptoms according to DEMS scores (Table 5 & Figure 3). Although there is no standard guideline for frequency of visits for managing dry eye, clinicians tend to space visits out when a desired level of symptom control has been reached. According to our data, however, waiting for longer periods of time between visits may increase the likelihood of worsening of symptoms. But because the DEMS ask patients to consider their symptoms over the past week, a large variation in symptoms over time may make this association difficult to establish. Another study is required to determine how the length of time between visits actually affects disease management and patient-reported symptom burden.

Although this study has some minor, yet significant, limitations, it is certainly not without strengths. By using patients seen by the same provider, I can be more certain that clinical assessments of dry eye disease were more equal, valid and reliable from patient to patient and may be why we were able to obtain modest correlations between

signs and symptoms. By recruiting patients at their normally scheduled appointments, I also had the advantage of having different follow-up times between visits. This allowed me to see the responsiveness of the DEMS over different lengths of time and within the natural clinical setting and disease course.

I am also confident that in this small feasibility study for establishing the MCID we were able to demonstrate that the UNC DEMS is in fact a responsive PRO instrument that can be used to aid physicians' therapeutic strategies for dry eye disease over time. Modest, statistically significant correlations with clinical tests of disease severity also demonstrate further validity of the UNC DEMS as a meaningful health outcome measure. Another, larger study will validate my estimation of the MCID and may provide further insight into how to better manage patients with dry eye disease. Although I conducted this study with only English speaking patients, a colleague is also currently developing and validating a Spanish version of the UNC DEMS. Future research will involve validity and outcomes studies across multiple providers and centers for both English and Spanish versions of the DEMS.

REFERENCES

1. Bottomley A, Jones D, Claassens L. Patient-reported outcomes: assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. *Eur J Cancer*. 2009;45(3):347–53. doi:10.1016/j.ejca.2008.09.032.
2. Reeve BB, Burke LB, Chiang Y, et al. Enhancing measurement in health outcomes research supported by Agencies within the US Department of Health and Human Services. *Qual Life Res*. 2007;16 Suppl 1:175–86. doi:10.1007/s11136-007-9190-8.
3. Revicki DA. FDA draft guidance and health-outcomes research. *Lancet*. 2007;369:540–542.
4. Selby J V, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. *JAMA*. 2012;307(15):1583–4. doi:10.1001/jama.2012.500.
5. Nichols KK. Patient-Reported Symptoms in Dry Dye Disease. *Ocul Surf*. 2006;4(3):137–145. doi:10.1016/S1542-0124(12)70040-X.
6. Miljanovic B, Dana R, Sullivan DA, Schaumberg D a. Impact of dry eye syndrom on vision-related quality of life. *Am J Ophthalmol*. 2007;143(3):409–415.
7. Mertzanis P, Abetz L, Rajagopalan K, et al. The relative burden of dry eye in patients' lives: comparisons to a U.S. normative sample. *Invest Ophthalmol Vis Sci*. 2005;46(1):46–50. doi:10.1167/iovs.03-0915.
8. Schaumberg D a, Sullivan D a, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol*. 2003;136(2):318–326. doi:10.1016/S0002-9394(03)00218-6.
9. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of Dry Eye Disease Among US Men. 2013;127(6):763–768.
10. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. *Ophthalmology*. 2003;110(7):1412–9. doi:10.1016/S0161-6420(03)00462-7.
11. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea*. 2004;23(8):762–70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15502475.
12. Khadka J, McAlinden C, Pesudovs K. Quality assessment of ophthalmic questionnaires: review and recommendations. *Optom Vis Sci*. 2013;90(8):720–44. doi:10.1097/OPX.0000000000000001.
13. Guillemin I, Begley C, Chalmers R, Baudouin C, Arnould B. Appraisal of patient-reported outcome instruments available for randomized clinical trials in dry eye: revisiting the standards. *Ocul Surf*. 2012;10(2):84–99. doi:10.1016/j.jtos.2012.01.007.
14. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol*. 2000;118(5):615–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10815152.
15. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol*. 2010;128(1):94–101. doi:10.1001/archophthalmol.2009.356.
16. Abetz L, Rajagopalan K, Mertzanis P, Begley C, Barnes R, Chalmers R. Development and validation of the impact of dry eye on everyday life (IDEEL) questionnaire, a patient-reported outcomes (PRO) measure for the assessment of

the burden of dry eye on patients. *Health Qual Life Outcomes*. 2011;9(1):111. doi:10.1186/1477-7525-9-111.
17. Fairchild CJ, Chalmers RL, Begley CG. Clinically Important Difference in Dry Eye : Change in IDEEL-Symptom Bother. 2008;85(8):29–34.
18. Grubbs JR, Tolleson-Rinehart S, Huynh K, Davis RM. A review of quality of life measures in dry eye questionnaires. *Cornea*. 2014;33(2):215–8. doi:10.1097/ICO.0000000000000038.
19. Ocular Surface Disease Index. (D). Available at: dryeyezone.com/encyclopedia/documents/OSDI.pdf. Accessed May 29, 2014.
20. Mokkink LB, Terwee CB, Knol DL, et al. Protocol of the COSMIN study: COnsensus-based Standards for the selection of health Measurement INstruments. *BMC Med Res Methodol*. 2006;6:2. doi:10.1186/1471-2288-6-2.
21. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res*. 2010;19(4):539–49. doi:10.1007/s11136-010-9606-8.
22. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11(2):163–169. doi:10.1586/erp.11.12.
23. Patrick DL, Burke LB, Powers JH, et al. Patient-reported outcomes to support medical product labeling claims: FDA perspective. *Value Health*. 2007;10 Suppl 2:S125–37. doi:10.1111/j.1524-4733.2007.00275.x.
24. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10(4):407–15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2691207.
25. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc*. 2002;77(4):371–83. doi:10.1016/S0025-6196(11)61793-X.
26. Wyrwich KW, Bullinger M, Aaronson N, Hays RD, Patrick DL, Symonds T. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res*. 2005;14(2):285–95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15892420.
27. Foulks GN, Lemp M. 2007 Report of the International Dry Eye WorkShop (DEWS). *Ocul Surf*. 2007;5(2):1–204.

TABLES

Table 1. Participant characteristics

Characteristic	All participants (N = 33)
Sex, No. (%)	
Male	10 (30.3)
Female	23 (67.7)
Age, mean (SD, range)	60.5 (13.9, 32-83)
Days since last DEMS, mean (SD, range)	122.5 (67.0, 25-244)
Most Recent DEMS, mean (SD, range)	5.33 (1.97, 2-9)

SOURCE: data collected by first author for the UNC DEMS MCID study.

Table 2. Correlation of the DEMS score change with independent variables

Variable	Correlation with DEMS score change
Global Change Assessment	-0.4229 (p = 0.014)
Age	-0.1042 (p = 0.564)
Sex	+0.3081 (p = 0.081)
Days since last DEMS	+0.5069 (p = 0.003)
Last DEMS score	-0.3741 (p = 0.032)

SOURCE: data collected by first author for the UNC DEMS MCID study.

Table 3. DEMS score change by patient-reported Global Change Assessment

Change category	**N of cases**	**Mean change, DEMS score (SD)**
The Same	8	+0.44 (1.05)
A little better/worse	11	-1.09 (1.32)
Somewhat better/worse	8	-1.81 (1.58)
Much better/worse	6	-1.00 (2.37)

SOURCE: data collected by first author for the UNC DEMS MCID study.

Table 4. Participant perceptions of DEMS changes

Category	**Mean (SD, range)**
Smallest Improvement	2.0 (0.95, 1-4.5)
Smallest Worsening	2.3 (1.27, 1-4.5)
Goal Score	1.4 (0.77, 1-3)

SOURCE: data collected by first author for the UNC DEMS MCID study.

Table 5. Mean DEMS score change by days since last visit

Group	No.	Mean (SD, CI)
≥120 Days	14	0.17 (1.49; -0.681, 1.04)
<120 Days	19	-1.45 (1.64, -2.24, -0.657)
		p = 0.006

SOURCE: data collected by first author for the UNC DEMS MCID study.

Table 6. Mean DEMS score at last visit

Group	No.	Mean (SD, CI)
≥120 Days	14	4.4 (2.03; 3.26, 5.60)
<120 Days	19	6.0 (1.68, 5.19, 6.81)
		p = 0.021

SOURCE: data collected by first author for the UNC DEMS MCID study.

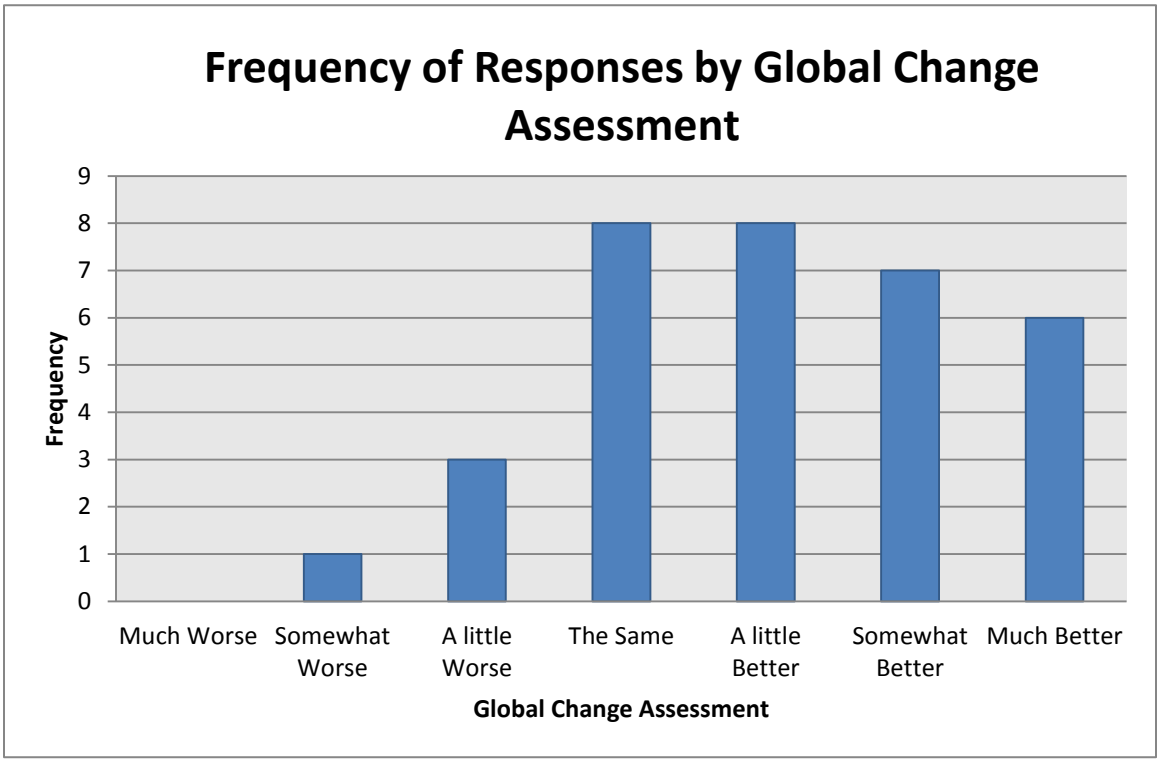
Table 7. Correlation between DEMS score and clinical assessment of disease severity (Spearman's Rank Correlation for non-normal distribution)

Clinical Test	Correlation with Current DEMS
Schirmer Tear Production Test	-0.4045 (p = 0.0266)
Oxford Grading Scheme	+0.3713 (p = 0.0364)
Tear Break-up Time	-0.3559 (p = 0.0456)

SOURCE: data collected by first author for the UNC DEMS MCID study.

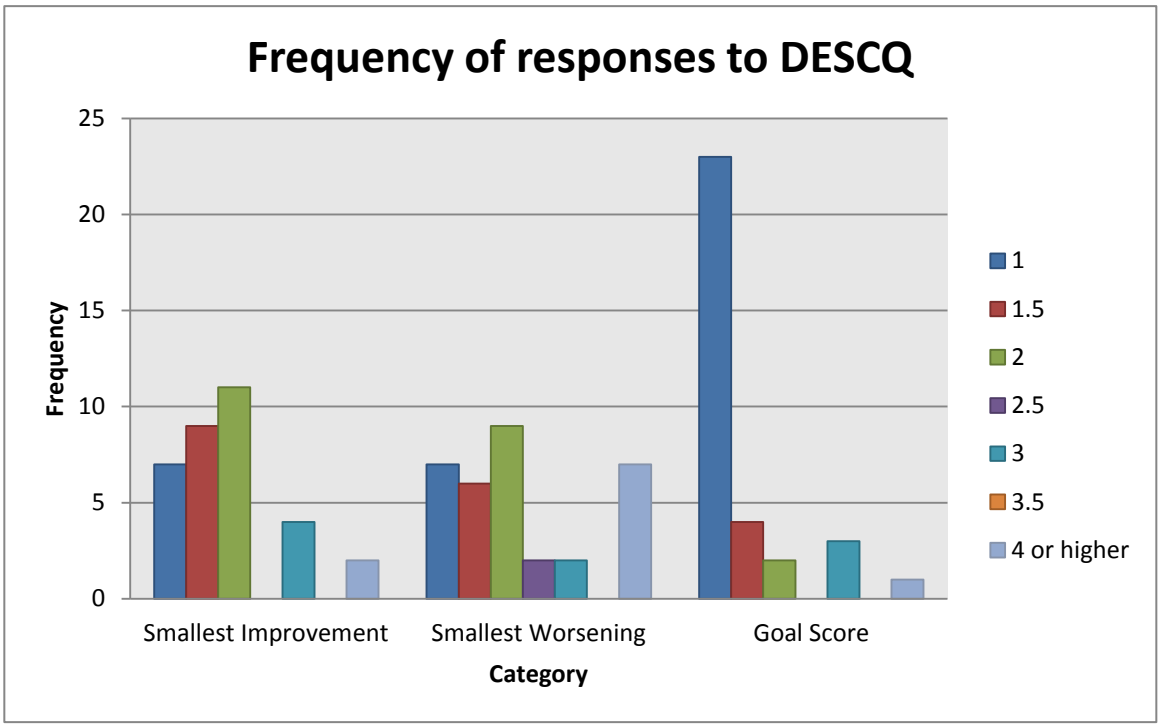
FIGURES

Figure 1. Frequency plot of Global Change Assessment responses



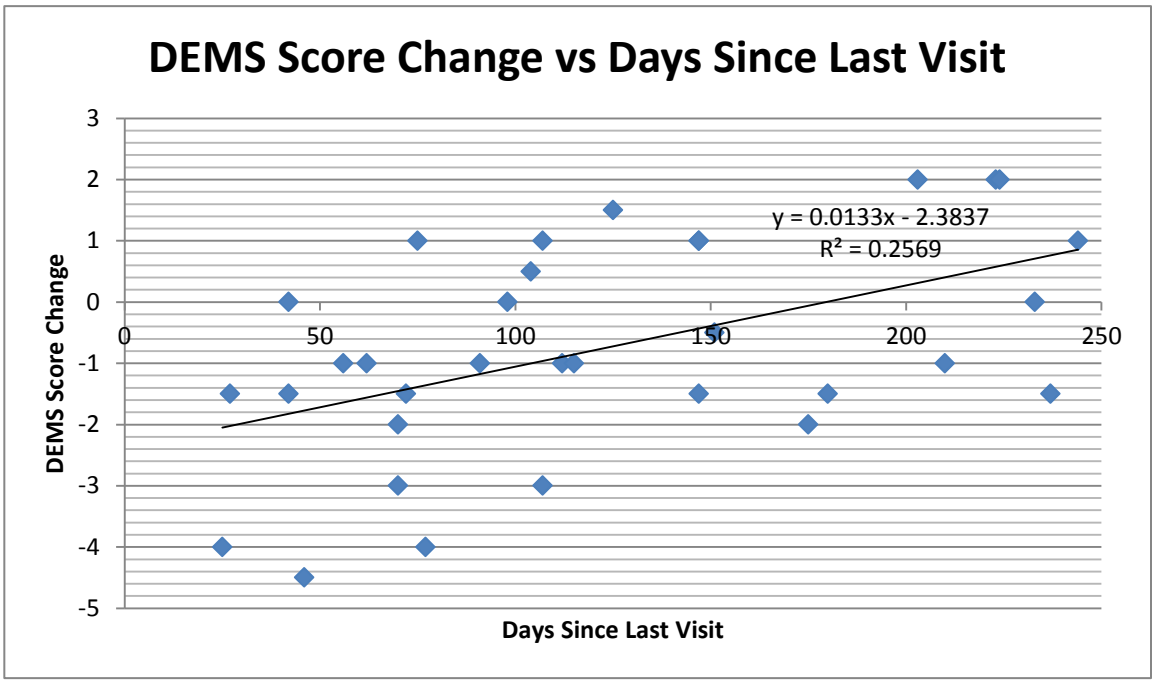
SOURCE: data collected by first author for the UNC DEMS MCID study.

Figure 2. Frequency of responses to DESCQ



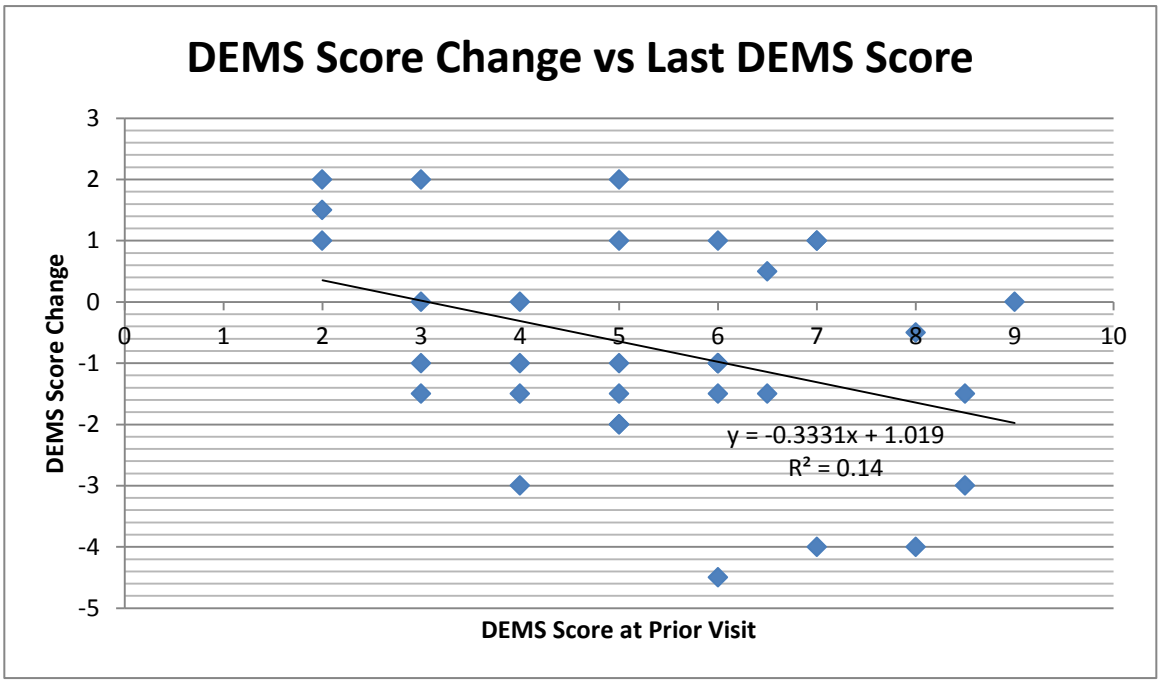
SOURCE: data collected by first author for the UNC DEMS MCID study.

Figure 3. Plot of change in DEMS score vs. days since last visit



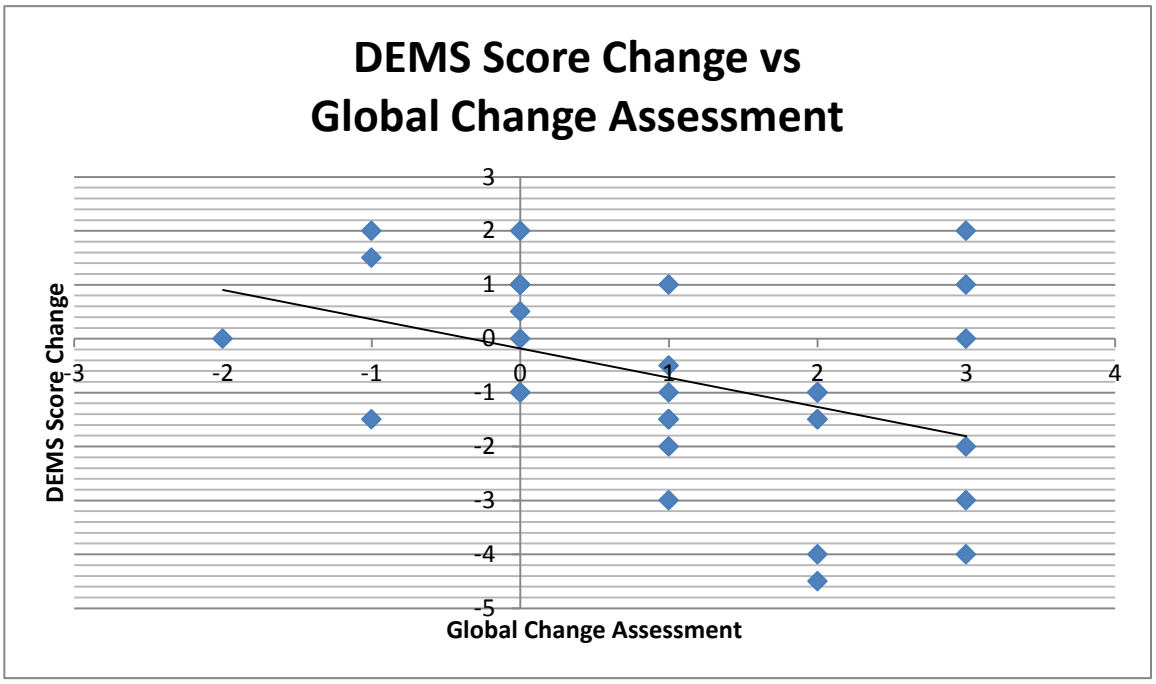
SOURCE: data collected by first author for the UNC DEMS MCID study.

Figure 4. Plot of change in DEMS score vs. last DEMS score



SOURCE: data collected by first author for the UNC DEMS MCID study.

Figure 5. DEMS score change vs. Global Change Assessment



SOURCE: data collected by first author for the UNC DEMS MCID study.

APPENDIX A: Systematic Review

Establishing the Minimal Clinically Important Difference in Patient Reported Dry Eye Questionnaires: A Systematic Review of Methods

INTRODUCTION

The International Dry Eye WorkShop (DEWS) defines dry eye disease (DED) as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface."[1] Symptoms often include, but are not limited to, ocular pain, burning, tearfulness, grittiness, and photophobia.[2] DED affects about 1.68 million men and 3.23 million women older than age 50.[3,4] Although DED is more prevalent in older populations, DED can occur in younger patients and has an estimated 5% to 30% of the population at various ages in the United States.[5] Risk factors associated with DED include increasing age, female sex, hormonal changes, systemic autoimmune disease, diabetes mellitus and eye-related pathology.[6] Research has demonstrated that DED diminishes an individual's quality of life (QOL), hindering the ability to carry out daily activities such as reading, computer use and work-related tasks, leading to significant lost productivity each year.[6] Importantly, research has shown that QOL decreases as DED severity increases.[7] Utility assessments using time trade-off (TTO) methods have found that moderate to severe dry eye scores very similarly to other chronic conditions such as dialysis, severe angina and hip fractures.[8]

Further complicating the burden of disease is the lack of correlation between the severity of clinical findings with the symptoms described by patients with DED. Current clinical assessments of dry eye include tests of tear production and determination of ocular surface damage, however neither are reliable indicators of the severity of symptoms, leading to reliance on symptom-based diagnoses of DED.[9] DED is a chronic

condition that is currently without a cure. Therefore, therapies for DED are palliative rather than curative and revolve around improving tear production or decreasing evaporative loss of tears, which can be achieved through use of pharmacologic agents and/or lifestyle modifications.[10] However, the lack of correlation between clinical signs and symptoms of the disease makes assessment of treatment effectiveness difficult, which places great importance in the use of valid and reliable patient-reported outcomes (PRO) instruments for managing dry eye disease.

Evaluating PROMs

Recognition of the importance of PRO measures has increased considerably over the past two decades and has led to the emergence of numerous patient-reported outcome measures (PROMs). PROMs intended to measure quality of life have garnered particular attention, especially for use within research and clinical trials. As a result, several groups have developed criteria for evaluating PRO instruments. The Scientific Advisory Committee (SAC) of the Medical Outcomes Trust was commissioned to develop a set of attributes and review criteria for evaluating instruments used in measuring quality of life.[11] The COSMIN checklist has been well regarded as the standard for appraising psychometric properties of PROMs and includes the following measures: internal consistency, reliability, measurement error, content validity, structural validity, hypothesis testing, cross-cultural validity, criterion validity, responsiveness, and interpretability.[12] Since PROMs are now more widely used in clinical trials for support of drug labeling claims, the Food and Drug Administration has also provided guidance for use of PROMs and criteria for their evaluation.[13]

However, the utility of the PROMs goes beyond its psychometric properties and attributes, especially in the clinical setting where interpretability of these measures is influential in managing patient symptoms and therapies as in dry eye disease. The FDA

created the Study Endpoints and Label Development (SEALD) group to help with interpreting results of PROMs. Although their guidance is aimed toward the use of PROMs in research, the use of PROMs in the clinical setting can also benefit from established criteria for interpretability. The SEALD group has recommended establishing what is called the "minimal clinically important difference" (MCID) also referred to as the "minimal important difference" (MID), "minimally important change" (MIC) and other labels. The MCID in essence reflects "a score change in a measure, experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit."[14] There are currently two broadly accepted methods for determining the MCID: anchor-based methods, and distribution based methods, however these is no consensus for preferred or stronger method.[15–17] Instead, experts agree that a combination of methods may provide the best estimation of MCID for a questionnaire or scale.

Current state of the dry eye PROM literature

The MCID is established in order to assess a questionnaires' responsiveness. Although responsiveness is included in the COSMIN checklist as important criteria for questionnaire validity, it is often left out of validation studies, particularly within the field of ophthalmology.[18] Two review papers were recently published evaluating existing questionnaires used in ophthalmology. In a review by Khadka and colleagues, the authors appraised all existing ophthalmology PRO questionnaires for their psychometric properties and validity, including responsiveness.[18] However, the authors only included three dry eye questionnaires: the Ocular Surface Disease Index (OSID), the Ocular Comfort Index (OCI), and McMonnies questionnaire.

In another review by Guillemin and colleagues, the authors aimed to appraise all dry eye PRO instruments for use in clinical trials and also included responsiveness in

their appraisal. Out of 18 identified dry eye questionnaires, the authors reported responsiveness assessments for only 5 of the questionnaires. Neither of the articles reports the methods for how the MCID was established for each questionnaire, nor do they attempt to evaluate the soundness of the methods. Another paper published this year by my colleagues at UNC reviewing the quality of life measures in dry eye questionnaires identified only two questionnaires (OSDI & IDEEL) suited to measure QOL. However, the authors chose not to focus on evaluating the methods used in the questionnaires responsiveness or establishing an MCID.[19]

Therefore, no comprehensive systematic review of the methods used for determining the MCID or responsiveness in ophthalmology questionnaires currently exists. While PROMs can be extremely useful for assessing patient symptom burden or quality life as it relates to dry eye, if a PROM is unable to detect a change over time, or nothing is known about the MCID, then the utility for assessing disease severity in order to make clinical or therapeutic adjustments is greatly diminished. In order to help providers understand the utility of the questionnaires they use to manage care for patients with dry eye, we need to know which questionnaires have an established MCID as well as an evaluation of the methods used to determine the MCID.

METHODS

Key Questions

This review attempts to answers the following questions:

Key Question 1: Which validity and reliability studies for questionnaires used in the evaluation of symptoms or health-related quality of life in patients with dry eye disease have established a minimal clinically important difference (MCID)?

Key Question 2: Which methods are most commonly reported to determine the MCID?

Key Question 3: Which studies have assessed responsiveness based on the established MCID?

Eligibility criteria

Because responsiveness, which includes establishing an MCID, should be established during development or validation of a questionnaire, the eligibility criteria were developed to capture any literature involving the development of patient-reported questionnaires or their validation. Studies that independently determine the MCID of an existing questionnaire were also intended for capture. To be included for review, studies must have focused on either questionnaire development, assessment of psychometric properties, and/or questionnaire validity/reliability. Articles based on studies of questionnaires not related to dry eye, or not based on patient-reported symptoms or HRQOL were excluded. Language or cultural adaptation validation studies for existing questionnaires are beyond the scope of reviewing methods for determining responsiveness and were also excluded. Questionnaires meant solely for diagnosis of

dry eye disease were also excluded because these questionnaires are not intended for repeated use over time in the same patient. Since the goal of this review is to assess the state of the questionnaire validation methods, which should include responsiveness but may not, I did not exclude studies based on the methods, quality, or results of the studies.

Search Strategy

I conducted a systematic search of PubMed with a last search date of April 24, 2014. With the help of a research librarian, I developed and used the following search strategy: "((patient reported[tiab] OR patient-reported[tiab] OR PRO[tiab] OR PROM[tiab] OR quality of life[MeSH] OR HRQOL[tiab] OR VRQOL[tiab] OR quality of life[tiab]) AND (questionnaires[MeSH] OR questionnaire[tiab] OR scale[tiab] OR instrument[tiab]) AND (development[tiab] OR reliability[tiab] OR validity[tiab] OR validation[tiab] OR "responsiveness" OR MCID[tiab] OR psychometrics[MeSH]) AND (ophthalmology[MeSH] OR ophthalmology[tiab] OR dry eye syndromes[MeSH] OR dry eye[tiab] OR ocular surface[tiab]))". Search results were restricted by language to include only articles published in English. No other search filters were used. I also conducted individual searches for any validation or MCID literature related to each questionnaire include in the DEWS and the paper by Guillemin and colleagues.

Study selection

I screened all search results by title and abstract for eligibility and inclusion based on the criteria aforementioned and summarized in Table 1. Any article for which sufficient information to determine eligibility was lacking then underwent full-text analysis for eligibility. All articles deemed eligible for inclusion then underwent full-text review. I was the only reviewer. The study selection process is summarized in Figure 1.

Table 1. Modified PICOTS Eligibility Criteria:

	Inclusion	Exclusion
Population	Studies reporting the development of questionnaires to be used in patients with dry eye disease to assess symptoms or quality of life Studies specifically done to establish the MCID	Studies not related to dry eye questionnaires Studies for questionnaires meant solely for diagnosis of dry eye Studies of questionnaires not based on patient-reported symptoms/quality of life
Intervention	Method for determining MCID/responsiveness	
Outcome	Quality of methods for determining MCID/responsiveness	
Time Frame	Any	
Study Design	Questionnaire validation studies; methodological studies	Non-validation or non-methodological studies; validation studies for language or cultural adaptation of existing questionnaires

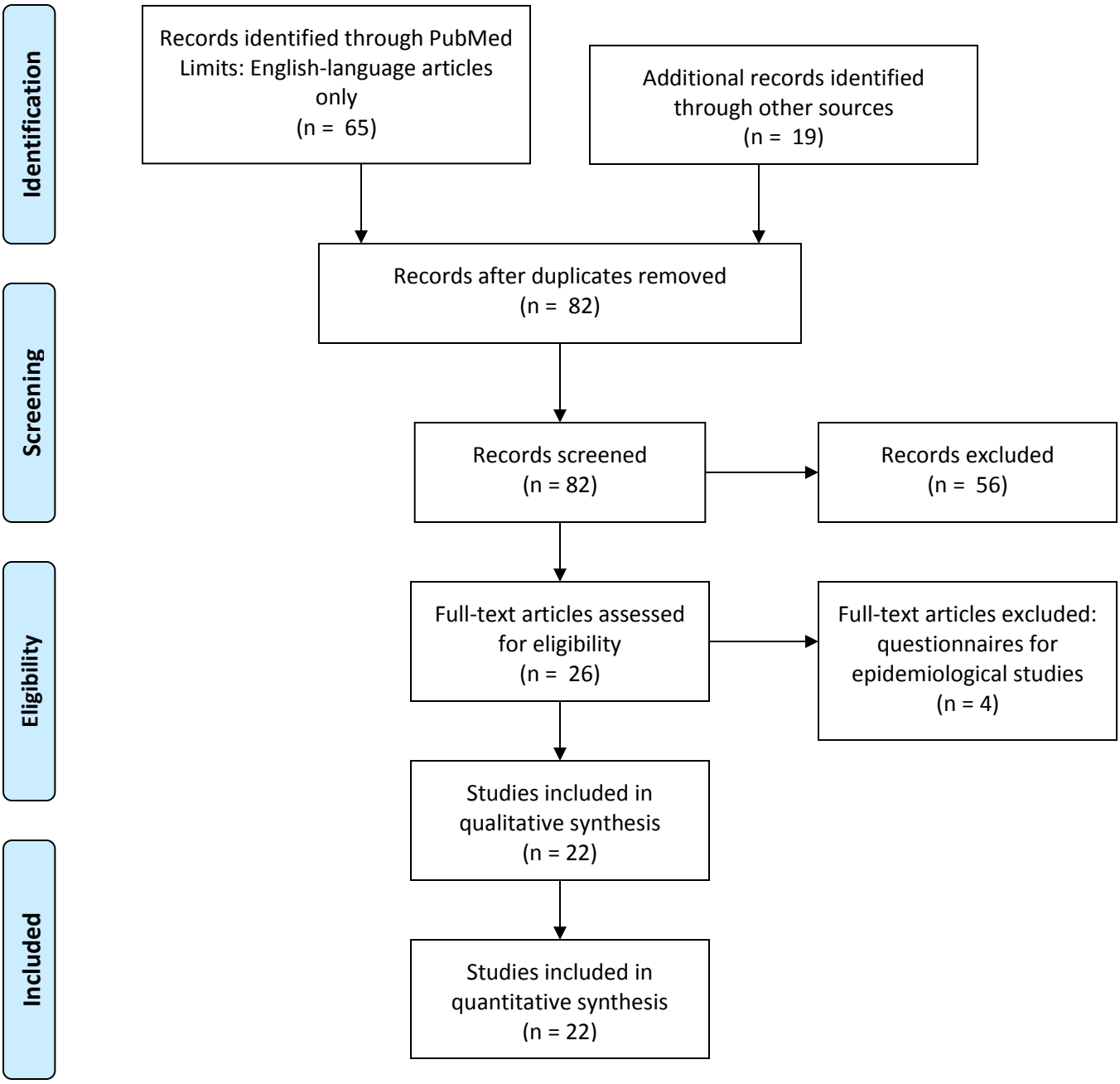
Data Extraction

To collect data, I developed a data extraction sheet to gather the following information from each article: intended purpose for questionnaire development and use, responsiveness/MCID statistics, and responsiveness/MCID methods.

Data Synthesis and Method of Analysis

Studies were examined for information about questionnaires and their development, including the intended use of the questionnaires and the target population. All studies were also examined for reporting of psychometric or validity analysis and validity and reliability statistics were recorded when reported. I then assessed whether the study attempted to establish the MCID and what methods were used to do so. Data were recorded and organized by either ‘anchor-based methods’ or ‘distribution-based methods’ and then I evaluated the methods used. If the study did not mention of the MCID or responsiveness, the lack of data was also recorded in the data extraction sheet.

Figure 1. PRIMSA 2009 Flow Diagram for Study Selection



RESULTS

Literature search yielded 26 articles for full-text review for 21 different dry eye questionnaires. Of those 21 questionnaires, 4 were excluded because their intended use was for epidemiological studies (CANDEES, DEEP, Schein, and Women's Health Study) and not for clinical purposes.[6,20–23] Of the remaining 17 questionnaires, only the CLDEQ-8, DEQ, DEQS, IDEEL, and OSDI reported using the questionnaire to detect changes over time with just 3 of those reporting an actual estimation for a minimal clinically important difference – the DEQ, OSDI, and the IDEEL.[24–29] A list of the 17 questionnaires and their reasons for development are summarized in Table 3. The instruments that reported any data related to assessing change of symptoms over time are summarized in Table 4, with MCID included when reported.

CLDEQ-8

The CLDEQ-8 does not have an established or reported MCID. However, they did use the scale to assess symptom changes over a 2-week period in patients randomized to two different contact lenses. They were asked to report their overall perceptions of their current contact lenses, and those responses were used as anchors for grouping in ANOVA analysis. The authors considered a change in assessment by two steps to be "much worse" or "much better" depending on the associated direction of score change. They found that patients reporting a worse overall opinion (n=73) had a 8.5 +/-5.8 point increase, those unchanged (n=218) had a -2.3 +/-5.0 decrease, and those improved (n=11) had a -16.7 +/-10.0 decrease in score. The ANOVA determined that the distribution was significantly related to change in overall opinion ($F=16.5$, $p<0.001$). Again, the authors' findings may be important, but we are uncertain based on

Table 3. Instruments used for assessing symptoms, health-related quality of life (HRQOL), and/or visual functioning in patients with dry eye disease (DED) (n=17)

Acronym	Instrument Name	Reason for Development
CLDEQ[30]	Contact Lens Dry Eye Questionnaire	Examine distribution of symptoms (intensity & frequency) among contact lenses wearers
CLDEQ-8[31]	Contact Lens Dry Eye Questionnaire-8	Shorter 8-item version of CLDEQ
DEQ[25]	Dry Eye Questionnaire	Distinguish diagnosis of DED with Sjogren's Syndrome (SS) & without SS
DEQ-5[32 24]	Dry Eye Questionnaire-5	Shorter 5-tiem version of DEQ
DEQS[33]	Dry Eye Questionnaire	Assess symptom severity and effect on HRQOL
IDEEL[28,29]	Impact of Dry Eye in Everyday Life	Assess symptoms and HRQOL in three domains: HRQOL, treatment satisfaction, symptom bother
McMonnies[34]	McMonnies Dry Eye Questionnaire	Diagnose DED and assess risk factors for developing DED
NEI-VFQ25[35–37]	National Eye Institute Visual Function Questionnaire-25	Assess influence of vision on multiple dimensions of HRQOL
OCI[38]	Ocular Comfort Index	Assess severity of discomfort from DED for use in clinical trials
OSD[39]	Ocular Surface Disease	Assess symptoms, perception of treatment, and HRQOL
OSDI[26,27]	Ocular Surface Disease Index	Assess symptom severity and their effect on HRQOL in three domains: ocular symptoms, vision-related function, and environmental triggers
SANDE[40]	Symptom Assessment iN Dry Eye	Assess frequency and severity of symptoms
SSI[41]	Sicca Symptom Inventory	Assess severity of fatigue and general discomfort in Primary SS
SIDEQ[42]	Single Item Score Dry Eye Questionnaire	Assess ocular discomfort due to symptoms
SPEED[43]	Standard Patient Evaluation of Eye Dryness Questionnaire	Assess symptoms including diurnal and longer-term symptom changes
TERTC-DEQ[44]	Texas Eye Research and Technology Center Dry Eye Questionnaire	Assess symptoms, effects of symptoms on patients' occupation, and indicate specific sources of dry eye
n/a[45,46,47]	11-question Dry Eye Syndrome Questionnaire	Assess nature, severity and functional impact of symptoms to determine correlation with clinical tests

Tabel 4. Summary of instruments reporting MCID methods

Questionnaire	MCID	Methods	Population & Intervention	Follow-up time	Statistical analysis
CLDEQ-8	Not specified	Anchor-based: within patient global transition assessment "Which statement best describes your overall opinion of your current contact lenses: poor, fair good, very good, or excellent"	309 patients randomized to two different soft contact lenses (senofilcon A or lotrafilcon B silicone hydrogel)	2 weeks	ANOVA ($p<0.05$)
DEQ	>1 unit	Anchor-based: within patient global transition	48 normal and 162 DED patients; no data on intervention	2-weeks	Comparison of Cohen's Kappa ($p<0.05$)
DEQS	Not specified	Distribution-based?	10 patients who underwent punctual plug insertion	Not reported	2-tailed paired t-test ($p<0.05$)
IDEEL-SB (symptom bother module)	12-points; ES = 1.14	Anchor-based: within patient global transition assessment 5-point Likert scale from "much worse" to "much better"	75 non-contact lens wearers using artificial tears QID	Baseline, 1-week, & 4-weeks	ROC to determine optimal MCID (used collapsed data)
OSDI	7.0 to 9.9 overall; 4.5 to 7.3 for mild-moderate; 7.3-13.4 for severe disease	Anchor-based: within patient global transition assessment (SGA) and clinician global impression (CGI) Distribution-based: 0.5 SD, effect-size, standardized response mean	310 consecutive patients with "suppressed tear production" from RESTORE registry	SGA: 378.5 days (SD 348.7) CGI: 418.0 days (SD 349.5)	Linear regression coefficients to estimate MCID

their methods how meaningful these reported changes are. Another limitation is the large number of patients who reported no change, leaving much smaller sample sizes for those reporting improvement of worsening in their opinions, particularly for improvement. Furthermore, these global transition assessments only referred the their overall opinion of contact lens use, and not an impression of dry eye symptoms or their effects on quality of life.

DEQ

I was only able to find limited information on the development of the DEQ. The authors of a paper determining the repeatability of symptoms as captured by the DEQ reported finding that a >1 unit change in score should represent a "clinically significant treatment effect for use in clinical trials."[25] This reported MCID was determined by comparing Kappa values for those reporting no change in symptoms to those who reported change as a measure of "responsiveness." They found the PM intensity questions to be the most responsive with Kappa values for those reporting no change ranging from .361 (PM Tired Eyes) to .472 (PM Blurry Vision) compared to .133 (PM Dryness) to .181 (PM Tired Eyes) among patients reporting a change ($p<0.05$). Again, using changes in Kappa scores related to patient-reported global change is not commonly cited as a method of determining clinically meaningful changes using patient-reported questionnaires leaving readers with uncertainty of the true meaning of such a change in score.

DEQS

The DEQS is a recently developed questionnaire that is meant to address the effects of symptoms on HRQOL. The developers report the motivation for creating this questionnaire was to provide an instrument that can be easily used in routine clinical

practice and that also covers some of the shortcomings some have reported in the OSDI's ability to cover all relevant domains of DED (Citations, Khadka and DEQS). As part of the development, the authors assessed the following psychometric properties: internal consistency, reproducibility, discriminant validity, concurrent validity, and responsiveness. Although they acknowledge the importance of assessing the responsiveness of the instrument, they did not report or attempt to establish the MCID. Rather, they used within patient global assessment of change before and after punctual plug insertion and used paired t-tests to determine statistical significance to the differences in scores.

For changes in DEQS scores before and after punctual plug insertion the authors report statistically significant changes in all three subscales: impact on daily life (37.2 to 20.7; $p = 0.04$), bothersome ocular symptoms (49.6 to 19.3; $p < 0.001$), and summary score (42.1 to 20.0; $p = 0.001$). The authors also report statistically significant improvements in fluorescein staining and tear film breakup time. Although the improvements in score and clinical findings appear to represent modest improvements, the improvements in score are accompanied by large standard deviations due to small sample size of just 10 patients. The paired t-test still showed a statistically significant difference, however we are still left with the uncertainty of the meaningfulness of these improvements without having a patient-reported global transition assessment.

IDEEL-SB

The developers of the IDEEL and IDEEL-SB MCID used the suggested methods for determining a MCID. Using an anchor-based method for assessing patient global transitions, they report that a change in score by 12 points reflects a clinically meaningful improvement in patient-reported symptoms. In determining this MCID, rather than take an arbitrary average of the scores within each category of reported symptom change,

they used ROC analysis to determine the optimal MCID. They also justified their determination of a 12-point cutoff for MCID by comparing it to a 10% change in score (10-point difference) and the related effect sizes. They found that going from 10 to 12 points improved Kappa scores only marginally, but increased the effect size (EF) by 20% and thus chose the 12-point cutoff as the MCID. One consideration to make when evaluating their MCID is that they found no difference between scores at 1 week and at 4 weeks and decided to combine the data for the analysis. They also decided to collapse the data from 5 categories down to 3 by combining the "much" and "somewhat" categories due to low responses in some categories. As a result, the authors then provide the MCID under the assumption that 12-point improvement in score are equally meaningful anywhere along the scale's severity spectrum and does not differentiate between different severities.

OSDI

The OSDI had the most transparent reporting of methods for a study specifically for determining the MCID. Patients must have had a diagnosis of DED, currently use artificial tears daily, normally eyelid position and closure, and also must have been likely to complete all required follow-up visits. Patients were excluded if they used cyclosporine ophthalmic emulsion currently or in the past as well as any oral or topical ophthalmic cyclosporine use within the past 3 yrs. Additionally, if patients had a condition that was considered to potentially influence a physician's opinion in a way that resulted in risk for the patient or confounded the results, they were also excluded.

The authors used an anchor-based within patient global transition assessment (SGA) as well clinical global impressions (CGI) to establish and MCID. They also used distribution-based methods to verify their results. To accommodate for anticipated small numbers within the categories for worsening, the authors folded the data to then assess

the magnitude in score changes regardless of direction of change. They found their reported MCIDs to be corroborated by the 0.5-SD approach yielding an MCID of 9.8 with an effect size of 0.51 and standardized response mean of 0.57. However, because they decided to fold the data, the assumption for the MCID is that the change in score representing a worsening of patient-reported symptoms is equivalent to the change in score for an improvement. No explicit follow-up time was required, however the authors reported the mean follow-up time in days with the standard deviation for the overall group as well as by DED severity. Follow-up times were significantly longer than the other studies ranging from 295.4 days for SGA for patients with moderate DED up to 464.4 days for CGI for patients with normal eyes.

DISCUSSION AND COMPARISON OF QUESTIONNAIRES

Managing chronic disease such as dry eye disease using PRO measures and instruments requires that the PRO tool be capable of effectively detecting changes over time. Despite the importance of the responsiveness of a PRO instrument in such context, very few questionnaires developed for DED have had their responsiveness assessed and/or determined an MCID. Of those that have reported data for using a questionnaire to detect changes over time, even fewer have established an MCID according to accepted practices – the OSDI and IDEEL.

The CLDEQ-8 developers report that a statistically significant difference in scores could be detected based on patient global assessments after a 2-week period. Although the authors' findings may be important, we are uncertain based on their methods how meaningful these reported changes are based on statistical significance alone. Another limitation is the large number of patients who reported no change, leaving much smaller sample sizes for those reporting improvement of worsening in their opinions, particularly for improvement. Furthermore, these global transition assessments only referred the

their overall opinion of contact lens use, and not an impression of dry eye symptoms or their effects on quality of life.

Authors of the DEQ make the assertion based on their findings that a >1-point change would be a clinically important change in score that could be used in clinical trials. However, their assertion is based on a statistically significant difference in Kappa scores in those reporting a change in symptoms over time. Unfortunately, using changes in Kappa scores related to patient-reported global change is not commonly cited as a method of determining clinically meaningful changes using patient-reported questionnaires leaving readers with uncertainty of the true meaning of such a change in score.

The DEQS was developed to be an improvement based on shortcomings identified with the OSDI. The authors recognized the importance of being able to use the DEQS to detect treatment effects over time and included an assessment of responsiveness. Although the changes in score and clinical findings appear to represent modest improvements, the improvements in score are accompanied by large standard deviations due to small sample size of just 10 patients. The paired t-test still showed a statistically significant difference, however we are still left with the uncertainty of the meaningfulness of these improvements without having a patient-reported global transition assessment to serve as an anchor. Additionally, we are not provided with any information about the 10 patients included in the study and the lack of a control group also limits the certainty of the findings.

The authors who established the MCID of the IDEEL-SB used methods consistent with the accepted literature for determining an MCID of a patient-reported questionnaire. Using ROC analysis to determine the most appropriate cutoff for MCID and using multiple methods to support their results contributes to the strength of the study. However, one consideration to make when evaluating their MCID is that they

found no difference between scores at 1 week and at 4 weeks and decided to combine the data for the analysis. They also decided to collapse the data from 5 categories down to 3 by combining the "much" and "somewhat" categories due to low responses in some categories. As a result, the authors then provide the MCID under the assumption that 12-point improvement in score are equally meaningful anywhere along the scale's severity spectrum and does not differentiate between different severities. Lastly, the MCID has only been established for the Symptom Bother (SB) module. However, the authors do report use of the IDEEL-SB as a stand alone domain is still shown to be valid and reliable.

Determination of the MCID of the OSDI was conducted through multiple methods including anchor-based methods as well as distribution-based methods to corroborate their findings. This combination has been stated as possibly the most ideal method for establishing a meaningful MCID.[17] However, there are some limitations in the authors' reports. Because they decided to fold the data in anticipation of low sample sizes for the worsening categories, the assumption for the MCID is that a meaningful change in score is independent of the direction of change. In other words, one's score would have to change by the same amount to represent a meaningful improvement/worsening regardless of the direction of the change, which may or may not be accurate. Establishing an MCID for each disease severity category, which appears to be an important distinction, strengthens their conclusions.

CLOSING COMMENTS

The DEWS asserts that "clinically meaningful changes in questionnaire scores need to be defined."[48] However, after assessing the state of the literature of patient-reported instruments in dry eye disease, we find that very few have taken the steps towards defining such a change. Because DED management relies so heavily on

patient-reported symptoms, there is an enormous need for valid, reliable, and responsive PROMs. Unfortunately at this time, only 2 questionnaires have made a concerted effort to establish an MCID. Continued work needs to be done to establish the MCID for questionnaires that claim to be useful in the clinical setting. Without an MCID, many clinicians are left with little certainty with how to interpret changes in scores over time. Until these measures have been determined, their utility in the clinical setting as well as research is greatly limited.

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REFERENCES:

1. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye Workshop (2007). *Ocul Surf*. 2007;5(2):75–92.
2. Nichols KK. Patient-Reported Symptoms in Dry Dye Disease. *Ocul Surf*. 2006;4(3):137–145. doi:10.1016/S1542-0124(12)70040-X.
3. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of Dry Eye Disease Among US Men. 2013;127(6):763–768.
4. Schaumberg D a, Sullivan D a, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol*. 2003;136(2):318–326. doi:10.1016/S0002-9394(03)00218-6.
5. Lemp M a. Advances in understanding and managing dry eye disease. *Am J Ophthalmol*. 2008;146(3):350–356. doi:10.1016/j.ajo.2008.05.016.
6. Miljanović B, Dana R, Sullivan D a, Schaumberg D a. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol*. 2007;143(3):409–15. doi:10.1016/j.ajo.2006.11.060.
7. Mertzanis P, Abetz L, Rajagopalan K, et al. The relative burden of dry eye in patients' lives: comparisons to a U.S. normative sample. *Invest Ophthalmol Vis Sci*. 2005;46(1):46–50. doi:10.1167/iovs.03-0915.
8. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. *Ophthalmology*. 2003;110(7):1412–9. doi:10.1016/S0161-6420(03)00462-7.
9. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea*. 2004;23(8):762–70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15502475.
10. Pflugfelder SC, Solomon A, Stern ME, Ph D. The Diagnosis and Management of Dry Eye. 2000;19(5):644–649.
11. Aaronson N, Alonso J, Burnam A, et al. Assessing health status and quality-of-life instruments: attributes and review criteria. *Qual life Res*. 2002;11(3):193–205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12074258.
12. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res*. 2010;19(4):539–49. doi:10.1007/s11136-010-9606-8.
13. *Guidance for Industry Patient-reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Guidance for Industry*.; 2009:1–43.
14. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11(2):163–169. doi:10.1586/erp.11.12.
15. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10(4):407–15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2691207.
16. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc*. 2002;77(4):371–83. doi:10.1016/S0025-6196(11)61793-X.

17. Wyrwich KW, Bullinger M, Aaronson N, Hays RD, Patrick DL, Symonds T. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res*. 2005;14(2):285–95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15892420.
18. Khadka J, McAlinden C, Pesudovs K. Quality assessment of ophthalmic questionnaires: review and recommendations. *Optom Vis Sci*. 2013;90(8):720–44. doi:10.1097/OPX.0000000000000001.
19. Grubbs JR, Tolleson-Rinehart S, Huynh K, Davis RM. A review of quality of life measures in dry eye questionnaires. *Cornea*. 2014;33(2):215–8. doi:10.1097/ICO.0000000000000038.
20. Doughty M, Fonn D, RIchter D, Simpson T, Caffery B, Gordon K. A patient questionnaire approach to estimating the prevalence of dry eye symptoms in patients presenting to optometric practices across Canada. *Optom Vis Sci*. 1997;74(8):624–631.
21. Oden N, Lilienfeld D, Lemp M, Al. E. Sensitivity and specificity of a screening questionnaire for dry eye. *Adv Exp Med Biol*. 1998;438:807–20.
22. Schein OD, Tielsch JM, Muñoz B, Bandeen-Roche K, West S. Relation between Signs and Symptoms of Dry Eye in the Elderly. *Ophthalmology*. 1997;104(9):1395–1401. doi:10.1016/S0161-6420(97)30125-0.
23. Gulati A, Sullivan R, Buring JE, Sullivan D a, Dana R, Schaumberg D a. Validation and repeatability of a short questionnaire for dry eye syndrome. *Am J Ophthalmol*. 2006;142(1):125–131. doi:10.1016/j.ajo.2006.02.038.
24. Begley CG. The Relationship between Habitual Patient-Reported Symptoms and Clinical Signs among Patients with Dry Eye of Varying Severity. *Invest Ophthalmol Vis Sci*. 2003;44(11):4753–4761. doi:10.1167/iovs.03-0270.
25. Chalmers RL, Begley C, Vistakon C. Repeatability of Habitual Symptoms as Measured by the Dry Eye Questionnaire. 2004;293:86–87.
26. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol*. 2000;118(5):615–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10815152.
27. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol*. 2010;128(1):94–101. doi:10.1001/archophthalmol.2009.356.
28. Abetz L, Rajagopalan K, Mertzanis P, Begley C, Barnes R, Chalmers R. Development and validation of the impact of dry eye on everyday life (IDEEL) questionnaire, a patient-reported outcomes (PRO) measure for the assessment of the burden of dry eye on patients. *Health Qual Life Outcomes*. 2011;9(1):111. doi:10.1186/1477-7525-9-111.
29. Fairchild CJ, Chalmers RL, Begley CG. Clinically Important Difference in Dry Eye : Change in IDEEL-Symptom Bother. 2008;85(8):29–34.
30. Nichols JJ, Mitchell GL, Nichols KK, Ph D, Chalmers R, Begley C. The Performance of the Contact Lens Dry Eye Questionnaire as a Screening Survey for Contact Lens-related Dry Eye. 2002;21(5):469–475. doi:10.1097/01.ICO.0000016340.19018.C6.
31. Chalmers RL, Begley CG, Moody K, Hickson-Curran SB. Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) and opinion of contact lens performance. *Optom Vis Sci*. 2012;89(10):1435–42. doi:10.1097/OPX.0b013e318269c90d.
32. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): Discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Cont Lens Anterior Eye*. 2010;33(2):55–60. doi:10.1016/j.clae.2009.12.010.

33. Sakane Y, Yamaguchi M, Yokoi N, et al. Development and validation of the Dry Eye-Related Quality-of-Life Score questionnaire. *JAMA Ophthalmol*. 2013;131(10):1331–8. doi:10.1001/jamaophthalmol.2013.4503.
34. Nichols KK, Nichols JJ, Mitchell GL. The reliability and validity of McMonnies Dry Eye Index. *Cornea*. 2004;23(4):365–71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15097131.
35. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol*. 2001;119(7):1050–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11448327.
36. Vitale S, Goodman L a, Reed GF, Smith J a. Comparison of the NEI-VFQ and OSDI questionnaires in patients with Sjögren's syndrome-related dry eye. *Health Qual Life Outcomes*. 2004;2:44. doi:10.1186/1477-7525-2-44.
37. Zadnik K, Ph D, Mitchell GL. Performance and Repeatability of the NEI-VFQ-25 in Patients With Dry Eye. 2002;21(6):578–583. doi:10.1097/01.ICO.0000016353.01275.23.
38. Johnson ME, Murphy PJ. Measurement of ocular surface irritation on a linear interval scale with the ocular comfort index. *Invest Ophthalmol Vis Sci*. 2007;48(10):4451–8. doi:10.1167/iovs.06-1253.
39. Baudouin C, Creuzot-Garcher C, Hoang-Xuan T. Creating a specific diagnostic and quality-of-life questionnaire for patients with ocular surface disease. *J French Opthalmology*. 2003;26:119–30.
40. Schaumberg D a., Gulati A, Mathers WD, et al. Development and Validation of a Short Global Dry Eye Symptom Index. *Ocul Surf*. 2007;5(1):50–57. doi:10.1016/S1542-0124(12)70053-8.
41. Bowman SJ, Booth DA, Platts RG, Field A, Rostron J. Validation of the Sicca Symptoms Inventory for Clinical Studies of Sjögren's Syndrome. *J Rheumatol*. 2003;30(6):1259–1266.
42. Srinivasan S, Joyce E, Jones LW. Tear osmolality and ferning patterns in postmenopausal women. *Optom Vis Sci*. 2007;84(7):588–92. doi:10.1097/OPX.0b013e3180dc9a23.
43. Ngo W, Situ P, Keir N, Korb D, Blackie C, Simpson T. Psychometric properties and validation of the Standard Patient Evaluation of Eye Dryness questionnaire. *Cornea*. 2013;32(9):1204–10. doi:10.1097/ICO.0b013e318294b0c0.
44. Narayanan S, Miller WL, Prager TC, et al. The Diagnosis and Characteristics of Moderate Dry Eye in Non-Contact Lens Wearers. *Eye Contact Lens Sci Clin Pract*. 2005;31(3):96–104. doi:10.1097/01.ICL.0000140907.45705.E2.
45. Afonso AA, Monroy D, Stern ME, et al. Correlation of Tear Fluorescein Clearance and Schirmer Test Scores with Ocular. *Ophthalmology*. 1999;106(4):803–810.
46. Herrmann WA, Shah CP, von Mohrenfels CW, Gabler B, Hufendiek K, Lohmann CP. Tear film function and corneal sensation in the early postoperative period after LASEK for the correction of myopia. *Graefes Arch Clin Exp Ophthalmol*. 2005;243(9):911–6. doi:10.1007/s00417-005-1130-0.
47. Miljanovic B, Dana R, Sullivan DA, Schaumberg D a. Impact of dry eye syndrom on vision-related quality of life. *Am J Ophthalmol*. 2007;143(3):409–415.
48. Foulks GN, Lemp M. 2007 Report of the International Dry Eye WorkShop (DEWS). *Ocul Surf*. 2007;5(2):1–204.

APPENDIX B: Methods and Questionnaires

Dry Eye Symptom Change Interviewing Summary

After I had received IRB approval, I along with another medical student searched Dr. Davis' UNC ophthalmology clinic schedules for patients with dry eye disease who had at least one prior DEMS score. We recruited patients during their regularly scheduled appointment while they waited to be seen by their ophthalmologist. After consenting to participate, the patients were asked about their symptoms using the Dry Eye Symptom Change Questionnaire (DESCQ). We administered the questionnaire by reading the questions on the DESCQ to the patient and we recorded their answers on the questionnaire. If needed, patients were shown the DESCQ or UNC DEMS for further clarification of the questions. The interviews lasted approximately 5 minutes on average. Afterwards, patients underwent usual clinical assessment of dry eye disease, which included Schirmer test, Oxford grading scheme, and tear break-up time.

Dry Eye Symptom Change Questionnaire

First, we'd like to know about your dry eye symptoms. Please answer the following questions:

On the UNC DEMS you filled out today, you chose a score of: _____

1. *Compared to your last visit*, how are your dry eye symptoms *now*?

Much Worse	Somewhat worse	A little worse	The same	A little better	Somewhat better	Much better
☐	☐	☐	☐	☐	☐	☐

2. If your dry eye symptoms have changed, why do you think they have changed?
   If they've stayed the same, skip to question 3.

3. Since your last visit, what things have you done that have helped your eyes?

Now, these last questions are about the UNC DEMS questionnaire you've filled out.

On the UNC DEMS, you choose a number that shows what your symptoms are like. We are trying to understand how well that number can show a change in your symptoms.

4. How many points would your score have to change to show that you felt like your symptoms were getting *better*? That is, how much change would be a meaningful improvement in quality of life for you? _____

(please turn page over) →

5. And how many points would your score have to change to show that you felt like your symptoms were getting *worse*? That is, how much change would mean that your symptoms were making your quality of life worse? _____

6. Last question! If you could choose a number on the UNC DEMS that would be your *goal score* for treatment of your dry eyes – the place you'd like to get to – what would that number be? _____

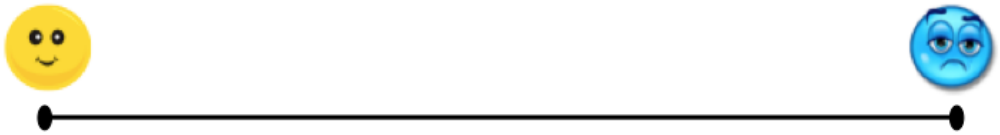
Thank you for your time! Your responses are very valuable and we appreciate your taking the time to fill this out!

UNC Dry Eye Management Scale

Instruction:
Your dry eye symptoms may include: *pain*, *burning*, *tearing*, *grittiness*, *"feeling like something is in your eye"*, and/or *sensitivity to light*.

We want to know how bad your dry eye symptoms are and how they affect your daily life and the things you want to do like reading, driving, working with a computer, watching TV, or doing things you enjoy.

Please circle the number (1-10) that ***best describes*** your dry eye symptoms and how **they affect** your daily life over the past week.



1 2 3 4 5 6 7 8 9 10

[1 - 2]
My symptoms are *not* a problem.

My dry eye *does not* affect my daily life at all.

[3 - 4]
My symptoms are *mild* and easily tolerable.

My dry eye *hardly* affects my daily life.

[5 - 6]
My symptoms are *moderately* bothersome.

My dry eye *sometimes* affects my daily life.

[7 - 8]
My symptoms are *very bothersome*.

My dry eye *frequently* affects my daily life.

[9 - 10]
My symptoms are *severe* and I need immediate medical care.

My dry eye *greatly* affects my daily life.

Is there anything else you would like your doctor to know about your eyes?